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Long-Term Efficacy and Tolerability of Flutamide Combined with Oral Contraception in Moderate to Severe Hirsutism: A 12-Month, Double-Blind, Parallel Clinical Trial

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Objective: Our objective was to test the efficacy and tolerability of three doses of flutamide (125, 250, and 375 mg) combined with a triphasic oral contraceptive (ethynylestradiol/levonorgestrel) during 12 months to treat moderate to severe hirsutism in patients with polycystic ovary syndrome or idiopathic hirsutism.

Design: We conducted a randomized, double-blind, placebo-controlled, parallel clinical trial.

Patients: A total of 131 premenopausal women, suffering from moderate to severe hirsutism, were randomized to placebo or 125, 250, or 375 mg flutamide daily associated with a triphasic oral contraceptive pill. Hirsutism (Ferriman-Gallwey), acne and seborrhea (Cremoncini), and hormone serum levels were monitored at baseline and at 3 (except hormone serum levels), 6, and 12 months. Side effects and biochemical, hematological, and hepatic parameters were assessed.

Methods: We used three-way ANOVA (subject, dose, and visit) with Scheffé adjustment for multiple comparisons or nonparametrical Friedman test and least-squares mean (paired data) and Kruskall-Wallis test for unpaired data analyses. We used χ^2 or Fisher's test for categorical data.

Results: A total of 119 patients were included in the intention-to-treat analysis. All flutamide doses induced a significant decrease in hirsutism, acne, and seborrhea scores after 12 months compared with placebo without differences among dose levels. Similar related side effects were observed with placebo and 125 mg flutamide (12.5%), and slightly higher with 250 mg (17.3%) and 375 mg (21.2%). No statistically significant differences were observed either among doses or compared with placebo.

Conclusions: Flutamide at 125 mg daily during 12 months was the minimum effective dose to diminish hirsutism in patients with polycystic ovary syndrome or with idiopathic hirsutism. **(*J Clin Endocrinol Metab* 92: 3446–3452, 2007)**

HIRSUTISM IS A COMMON disorder affecting 5–8% of the whole female population of fertile age (1, 2) and is defined as the presence of terminal (coarse) hairs in females in a male-like pattern (3). Hirsutism is a sign of increased androgen action on hair follicles, from increased bioavailable circulating androgen levels (either endogenous or exogenous) or from an increased sensitivity of the hair follicle unit to normal circulating androgen levels (4).

Etiology of the hirsutism can be familial or idiopathic, or it can be caused by excess androgen secretion by the ovary [*e.g.* polycystic ovary syndrome (PCOS) or adrenal glands (*e.g.* congenital adrenal hyperplasia and Cushing's syndrome) or an exogenous pharmacological source of androgens (5).

Treatment options can be classified in those for local manifestations (physical methods of hair removal) and those for the underlying causes. The latter is aimed at blocking the androgen action at hair follicles or at suppressing the androgen production (5, 6).

The available evidence suggests that cyclical oral contraceptives, spironolactone, and cyproterone acetate are equally effective, producing subjective and objective improvement in 50–60% of patients at 6 months. Side effects are not uncommon, and many patients discontinue treatment. Moreover, the administration of oral contraceptives can change the metabolic and lipid evolution depending on the dose of estrogen, type of progestin, and formulation of the preparation (7).

The most commonly used antiandrogens are spironolactone and flutamide. Flutamide, a nonsteroidal drug usually prescribed for prostatic cancer, is a pure peripheral androgen antagonist with no progestogenic or antigonadotropic action and thus does not cause menstrual irregularity (8). The clinical evidence shows flutamide as an effective drug for

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Abbreviations: DHEAS, Dehydroepiandrosterone sulfate; OC, oral contraceptive; PCOS, polycystic ovary syndrome.

women with idiopathic hirsutism or with a PCOS (9–13); however, liver toxicity might be a rare but potentially severe side effect of flutamide (14).

Until now, there is not much evidence to assess the clinical efficacy and tolerability of flutamide in double-blind, long-term, and placebo-controlled designs. To address this issue, 131 hirsute women were included in a 12-month course of double blind, placebo-controlled, randomized treatment with 125, 250, and 375 mg daily flutamide.

Subjects and Methods

Subjects

A total of 131 women of ages between 18 and 40 yr, who gave their written consent and had moderate to severe (a score of greater than 15 in the modified Ferriman-Gallwey scale) hirsutism of either idiopathic or PCOS etiology were included in the study by the 14 recruiting centers in Spain (safety population). Participation of patients in whom oral hormonal contraception was contraindicated was not considered. Patients who had received a diagnosis of iatrogenic hirsutism, ovarian or adrenal neoplasia, prolactinoma, Cushing's syndrome, congenital adrenal hyperplasia, diabetes mellitus, or thromboembolic disease were also excluded. Patients who had received treatment with oral hormonal contraceptives or systemic treatment of their hirsutism over the last 3 months or those who had started a cosmetic treatment for fewer than 30 d before inclusion were also excluded. Once patients had initiated the study, they were able to start cosmetic treatments based on hair shaving or bleaching, except during the 30 d before the visit for evaluation of their degree of hirsutism.

From the 131 patients included, 12 patients did not satisfy the inclusion criteria, and so, even though they were considered in the safety evaluation, they were excluded from the efficacy evaluation. A total of 119 patients were considered for the intention-to-treat analysis. Of these, the 77 women who completed the study with no major deviations formed the Per-Protocol population.

Study design

Patients were randomly assigned to one of the following: 1) placebo (control group), 2) 125 mg flutamide, 3) 250 mg flutamide, and 4) 375 mg flutamide, once daily during 12 months in association with a triphasic oral contraceptive (OC) pill (Triciclor, which is a triphasic treatment of 30, 40, and 30 μg ethynylestradiol and 50, 75, and 125 μg levonorgestrel). This study was carried out in double-blind conditions, and so neither the patient nor the doctor was aware of the composition of the treatment administered. For this purpose, preparation of the medication was performed in a centralized manner, and labeling, with the exception of the relevant randomization code, was identical in all four presentations.

The hair growth was estimated by a modification of the Ferriman-Gallwey scale (15) (Table 1) and the acne and seborrhea by the Cremoncini scale (16), in which for acne, a score of 1 indicates isolated pustules up to 10 in number, 2 indicates more than 10 isolated pustules, 3 indicates clusters of pustules, and 4 indicates confluent pustules; for seborrhea, 1 indicates mild, 2 moderate, and 3 severe. Scores for both scales

TABLE 1. Ferryman-Gallwey modified scale

Site and grade	Definition
1. Upper lip	
1	A few hairs at outer margin
2	A small moustache at outer margin
3	A moustache extending halfway from outer margin
4	A moustache extending to mid-line
2. Cheek	
1	A few scattered hairs
2	Scattered hairs with small concentrations
3	Light complete cover
4	Heavy complete cover
3. Chin	
1	A few scattered hairs
2	Scattered hairs with small concentrations
3	Light complete cover
4	Heavy complete cover
4. Chest	
1	Circumareolar hairs
2	Circumareolar hairs with mid-line hair in addition
3	Fusion of these areas, with three-quarter cover
4	Complete cover
5. Upper back	
1	A few scattered hairs
2	Some more, still scattered
3	Light complete cover
4	Heavy complete cover
6. Lower back	
1	A sacral tuft of hair
2	With some lateral extension
3	Three-quarter cover
4	Complete cover
7. Upper abdomen	
1	A few midline hairs
2	Some more, still mid-line
3	Half cover
4	Full cover
8. Lower abdomen	
1	A few midline hairs
2	A midline streak of hair
3	A midline band of hair
4	An inverted V-shaped growth

TABLE 2. Baseline characteristics of intention-to-treat population

	Placebo	Flutamide		
		125 mg	250 mg	375 mg
n	31	25	29	34
Age (yr)	24.1 (4.85)	24.0 (6.17)	24.6 (5.73)	24.7 (5.58)
Weight (kg)	66.3 (13.63)	66.7 (10.2)	71.0 (17.35)	68.7 (14.91)
Body mass index (kg/m^2)	25.4 (5.11)	25.2 (3.28)	26.9 (7.88)	27.3 (6.03)
Waist/hip index	0.78 (0.09)	0.81 (0.07)	0.80 (0.08)	0.79 (0.09)
Modified Ferriman-Gallwey score	18.4 (2.44)	19.3 (3.36)	18.7 (2.64)	18.0 (2.90)
Acne score	0.84 (1.10)	0.88 (0.88)	0.76 (1.15)	0.76 (1.02)
Seborrhea score	0.97 (0.84)	1.00 (1.00)	1.00 (1.04)	0.91 (1.03)

Results are shown as mean (SD).

were determined at baseline and at 3, 6, and 12 months. All measures relative to each patient were made by the same investigator. A standard hormonal profile, including serum levels of prolactin, estradiol, testosterone, dehydroepiandrosterone sulfate (DHEAS), androstenedione, 17α-hydroxyprogesterone, SHBG, free androgen index [total testosterone (nM)/SHBG (nM) × 100], LH, and FSH was assessed every 6 months. The hormone profile was centralized at one center (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain).

The safety evaluation comprised continuous adverse event assessment, monthly hematology and hepatic function evaluation, and a physical examination every 3 months. A biochemistry evaluation was also included every 6 months.

The study was conducted in accordance with the Declaration of Helsinki on human experimentation. The study protocol was approved by every local ethics committee of all the participant centers before the inclusion of the patients who gave written informed consent before any study procedure.

Monitoring visits were done at the recruiting centers to perform the source data verification following good clinical practice. A quality assurance plan was implemented for the protocol and all amendments, the case report form, the medication preparation and packaging, one of the participating centers (Hospital Juan Canalejo, La Coruña, Spain), the clinical study report, and the trial master file.

Statistics

The modified Ferriman-Gallwey hirsutism score and the Cremoncini acne and seborrhea scores were analyzed with a Friedman analysis and a least-squares mean multiple comparison approach (paired data) and with a Kruskall-Wallis analysis and Mann-Whitney *U* tests without any multiplicity adjustment (unpaired data). The laboratory parameters were analyzed with a three-way ANOVA (subject, treatment, and visit) and a Scheffé multiple comparison approach. The Shapiro-Wilk test was used to assess the normal distribution of the parameters. On the other hand, the categorical data were analyzed with a χ^2 or Friedman analysis. All significance tests were two tailed, and a test $P \leq 0.05$ was considered significant. An intent-to-treat approach was used with no replacement strategy for the missing data, and a sensitivity analysis was used for confirmation with the per-protocol population. The statistical analysis was performed with the SAS System version 8.

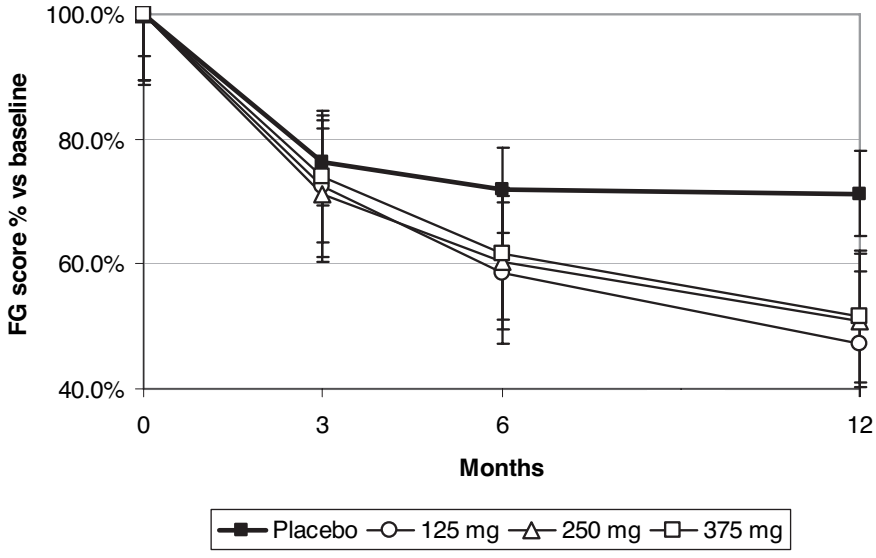

FIG. 1. Changes from baseline (percent) in the modified Ferriman-Gallwey (FG) hirsutism score [mean (SD)]. All treatment groups were associated with OCs.

	Day 0	Month 3	Month 6	Month 12
Placebo (n=31)	18.35 (2.44)	14 (5.23)	13.19 (5.5)	13.06 (5.71)
Flutamide 125 mg (n=25)	19.28 (3.36)	13.96 (5.03)	11.28 (5.2)	9.12 (5.14)
Flutamide 250 mg (n=29)	18.72 (2.64)	13.31 (4.57)	11.28 (4.22)	9.52 (4.93)
Flutamide 375 mg (n=34)	18 (2.9)	13.32 (4.61)	11.09 (5.22)	9.29 (5.58)

Results

The mean age was 24.4 yr (SD 5.5), the mean weight was 68.2 kg (14.34), and the mean weight/hip ratio was 0.80 (0.08).

Hirsutism

With no statistically significant differences at baseline in the Ferriman-Gallwey hirsutism score (Table 2), flutamide associated with an OC showed a significant hirsutism progressive decrease after 12 months of treatment compared with placebo associated with an OC ($P = 0.020$), with no differences among doses. At 12 months of treatment, the patients under placebo reduced their mean baseline hirsutism 28.8%, whereas patients under flutamide reduced it approximately 50% (52.7, 49.1, and 48.4% with 125, 250, and 375 mg, respectively) (Fig. 1). Although the placebo group showed a significant decrease at 6 months, it did not show any additional significant decrease at 12 months.

Acne and seborrhea

Although there were not statistically significant differences at baseline in the Cremoncini acne and seborrhea scores (Table 2), flutamide was associated with a significant improvement at 6 and 12 months for acne ($P = 0.031$ and $P = 0.002$, respectively) and at 6 months for seborrhea ($P = 0.012$). No differences were seen among doses. At 12 months, patients under placebo reduced their mean baseline acne by 46.4%, whereas patients under flutamide reduced it by over 80% (81.8, 86.8, and 88.2%, with 125, 250, and 375 mg, respectively) (Fig. 2). Although the mean seborrhea change from baseline to 6 months was statistically significant, it lost significance at 12 months. At 12 months, placebo improved seborrhea by 56.7% of the baseline seborrhea, whereas flutamide improved it by 88.0% with the 125-mg dose, 72.0% with the 250-mg dose, and 76.9% with the 375-mg dose (Fig. 3).

Endocrine features

All of the hormones profiled, except prolactin, showed a statistically significant change after the first 6 months of treatment (all hormone levels decreased, and SHBG increased) (Table 3). There were no significant differences among flutamide doses.

Tolerability

The incidence of adverse events possibly or probably related to the study drugs was similar between placebo and 125 mg flutamide (12.5%); even though not statistically significant, those incidences were higher with 250 mg (17.3%) and 375 mg (21.2%). The adverse events most frequently reported were upper respiratory tract infection (9.2%), dry skin (9.2%), headache (7.1%), nausea and vomiting (5.5%), and diarrhea (3.7%). One serious adverse event in the placebo group (sciatica aggravated not related to the study drug) occurred. On the other hand, there was one significant transaminase increase in the placebo group, another one with 250 mg flut-

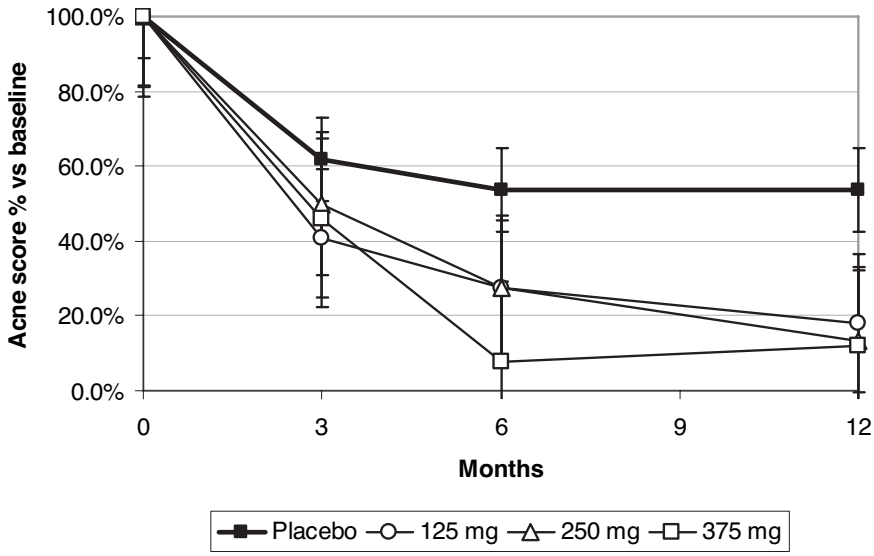

FIG. 2. Changes from baseline (percent) in the acne score [mean (SD)]. All treatment groups were associated with OCs.

	Day 0	Month 3	Month 6	Month 12
Placebo (n=31)	0.84 (1.1)	0.52 (0.81)	0.45 (0.77)	0.45 (0.72)
Flutamide 125 mg (n=25)	0.88 (0.88)	0.36 (0.81)	0.24 (0.72)	0.16 (0.55)
Flutamide 250 mg (n=29)	0.76 (1.15)	0.38 (0.78)	0.21 (0.62)	0.1 (0.56)
Flutamide 375 mg (n=34)	0.76 (1.02)	0.35 (0.77)	0.06 (0.24)	0.09 (0.29)

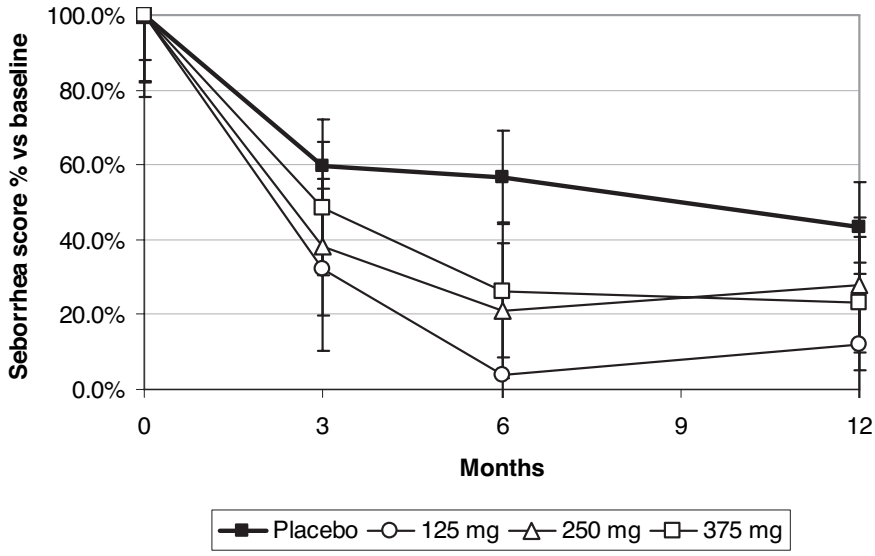

FIG. 3. Changes from baseline (percent) in the seborrhea score [mean (SD)]. All treatment groups were associated with OCs.

	Day 0	Month 3	Month 6	Month 12
Placebo (n=31)	0.97 (0.84)	0.58 (0.76)	0.55 (0.81)	0.42 (0.72)
Flutamide 125 mg (n=25)	1 (1)	0.32 (0.56)	0.04 (0.2)	0.12 (0.33)
Flutamide 250 mg (n=29)	1 (1.04)	0.38 (0.68)	0.21 (0.49)	0.28 (0.7)
Flutamide 375 mg (n=34)	0.91 (1.03)	0.44 (0.66)	0.24 (0.5)	0.21 (0.54)

amide, and another one with 375 mg flutamide. The 125-mg dose did not show any significant transaminase variation. No significant changes in mean transaminase levels were detected. From a total of 325 adverse events, 92.3% did not require any treatment change, 0.6% required a temporal treatment interruption, and 7.1% concluded in study withdrawals (4.6% with possible/probable relationship with the study drug). Among the most frequent adverse events according to systems or organs, the most frequent ones were gastrointestinal disorders (20.92% of the total adverse events), skin and appendix disorders (19.38%), respiratory tract disorders (18.15%), and vegetative nervous system disorders (10,46%). Individually, catarrh and flu syndrome were significant (9.23%) as well as dry skin (9.23%), headache (7.08%), nausea (5.54%), vomiting (5.54%), and diarrhea (3.69%).

Five women withdrew from the study due to clinically significant laboratory abnormalities (hematology assessed every month and biochemistry every 6 months): hyperglycemia not related to the treatment (placebo), leucopenia (250 mg flutamide) with relationship to study drug not assessed, and three episodes of transaminases increase possibly or probably related to the study drug (placebo, 250 mg flutamide, and 375 mg flutamide).

The physical examination did not show clinically relevant changes in the women's weight, waist to hip ratio, blood pressure, or heart rate.

Discussion

OCs are usually the first choice for the treatment of hirsutism for women who do not wish to become pregnant, but some maintain that all preparations are comparable in efficacy (17). These agents increase the level of SHBG and therefore decrease ovarian androgen biodisponibility while decreasing the risk of endometrial hyperplasia often seen in anovulatory women (9, 17).

For women with idiopathic hirsutism, PCOS, or late-onset congenital adrenal hyperplasia, childbearing plans should also be considered. This way, OCs containing less androgenic progestin, such as norgestimate, gestodene, and desogestrel, seem to be the best choice, because they increase the SHBG level and decrease the androgen bioavailability (9, 17). GnRH analogs should be reserved for use in women who do not respond to combination hormonal therapy or those who cannot tolerate OCs.

Spironolactone has been widely used for hirsutism, particularly in those women in whom estrogens are contraindicated. It is an aldosterone antagonist that has no suppressive effect on androgen levels but blocks androgen action through its ability to compete with testosterone and dihydrotestosterone by binding to the androgen receptor (18).

To diminish the limitation that implies the potential variability in hirsutism assessment judged by different investigators in this multicenter study, all measurements relative to each patient were obtained by the same investigator.

Although contraception pills were effective for hirsutism control as shown by the reduced Ferriman-Gallwey score in the placebo group, this study provides clear evidence of the increased efficacy induced by the addition of flutamide to oral contraception for the treatment of hirsutism either at 125, 250, or 375 mg compared with the placebo control group.

TABLE 3. Hormonal profile, at baseline and after 6 and 12 months

	Placebo	Flutamide		
		125 mg	250 mg	375 mg
n	31	25	29	34
Testosterone (nmol/liter)				
Baseline	2.15 (0.91)	2.21 (1.13)	2.46 (1.17)	2.28 (0.71)
Month 6	1.63 (0.61)	1.63 (0.68)	1.84 (0.96)	1.91 (0.75)
Month 12	1.64 (0.69)	2.05 (1.05)	1.87 (0.71)	2.10 (0.79)
SHBG (nmol/liter)				
Baseline	57.2 (41.00)	49.2 (52.21)	37.8 (23.69)	45.7 (47.4)
Month 6	93.6 (41.59)	183.6 (90.39)	161.3 (95.60)	165.8 (96.9)
Month 12	94.8 (52.22)	158.3 (70.39)	142.1 (103.27)	175.1 (103.23)
Free androgen index				
Baseline	5.06 (2.63)	7.58 (7.54)	8.09 (5.32)	7.12 (4.17)
Month 6	2.33 (2.09)	2.73 (7.39)	2.04 (2.42)	2.50 (4.20)
Month 12	2.86 (3.91)	2.96 (7.33)	2.68 (3.27)	2.40 (3.92)
Estradiol (nmol/liter)				
Baseline	0.14 (0.12)	0.13 (0.08)	0.16 (0.16)	0.13 (0.11)
Month 6	0.07 (0.04)	0.14 (0.26)	0.10 (0.17)	0.06 (0.06)
Month 12	0.07 (0.04)	0.07 (0.05)	0.07 (0.05)	0.13 (0.21)
DHEAS (nmol/liter)				
Baseline	7.62 (2.51)	7.07 (2.98)	7.85 (3.32)	6.91 (2.46)
Month 6	7.20 (2.63)	4.48 (2.08)	4.42 (1.75)	3.91 (1.94)
Month 12	6.55 (2.58)	4.48 (2.14)	4.32 (1.90)	3.81 (2.00)
Androstenedione (nmol/liter)				
Baseline	9.69 (3.83)	12,90 (6.98)	11.41 (3.79)	11.06 (4.12)
Month 6	7.56 (3.45)	8.33 (3.38)	7.66 (4.13)	8.60 (3.89)
Month 12	7.70 (3.38)	9.20 (5.31)	7.74 (3.55)	9.16 (4.37)
17OH-progesterone (nmol/liter)				
Baseline	2.85 (2.09)	2.93 (2.04)	2.69 (1.87)	3.01 (1.86)
Month 6	2.08 (1.75)	2.04 (1.88)	1.68 (0.98)	1.85 (1.08)
Month 12	1.90 (1.72)	2.06 (1.91)	1.69 (0.98)	1.83 (0.82)

Results are shown as mean (SD).

Flutamide reduced the modified Ferriman-Gallwey score by 52.7% (125 mg), 49.1% (250 mg), and 48.4% (375 mg) after 12 months of daily treatment, whereas the placebo control group reduced that score by only 28.8%. The improvement in the flutamide group was maintained during the whole 12-month period, whereas improvement with placebo was seen only during the first 6 months, being probably due to the associated OC treatment. No statistically significant differences were obtained for the different doses of flutamide.

We have found similar reductions in the Ferriman-Gallwey hirsutism scores in other previous studies with flutamide at higher different doses (ranging from 250–500 mg) (19–23). Moreover, our score reduction is even more than the highest reduction obtained by Muderris and colleagues with the 125-mg daily dose (24), with the 250-mg daily dose (23, 25), and with the 62.5-mg daily dose (26). For all those studies, however, we have found no differences among the flutamide doses tested.

In addition to the hirsutism score, we found a statistically significant reduction of the Cremoncini acne and seborrhea scores after 12 months of treatment, with a higher decrease up to 6 months compared with 12 months with the flutamide doses, as was found by other authors with the 250-mg dose (10, 11).

Our findings are in agreement with those published by others reporting a reduction in plasma levels of LH, FSH, estradiol, testosterone, androstenedione, and DHEAS (8, 21–23, 27, 28). We have also identified a decrease in 17OH-progesterone and the free androgen index. A significant part of these hormonal changes is the consequence of the blockade on the hypothalamic-pituitary-gonadal axis exerted by OCs. DHEAS, a metabolite predominantly adrenal in origin, also decreases with the three doses of flutamide. This can be because flutamide not only causes blockade of androgen receptors but also acts on the adrenals to reduce adrenal androgen synthesis (29, 30). On the other hand, SHBG serum levels were increased with all the tested doses, thus decreasing androgen bioavailability.

The tolerability of flutamide was good, with no differences in the incidences of adverse events possibly or probably related to the study drugs along the study period. Unlike other published results (21, 22), skin dryness probably related to the flutamide action mechanism inhibiting the sebum production was found in a lower incidence.

On the other hand, we did not find a significant liver toxicity (31, 32), with no significant transaminase variations in the 125-mg flutamide group, one significant transaminase increase in the placebo group, another with 250 mg flutamide, and another with 375 mg flutamide. However, because rare serious or even fatal hepatic side effects have been previously been reported with flutamide, adequate safety studies should be performed before advising for systematic coadministration of this product in the treatment of severe hirsutism.

In conclusion, this double-blind, placebo-controlled study shows that flutamide, even at the 125-mg dose, associated with OCs, is a very satisfactory therapeutic regimen in the treatment of hirsutism and better than OCs used alone. This association shows a very good safety profile, as evaluated only on changes in transaminase levels, and decreases the

risk of becoming pregnant during the antiandrogen treatment. Because the flutamide liver toxicity is dose dependent, the high risk/benefit ratio could be reduced by using the lower doses of this drug. Additional studies comparing the 62.5- and 125-mg flutamide daily doses could define the risk-benefit and cost effectiveness of these lower doses in the treatment of hirsutism to be used in place of high-dose flutamide, 250–750 mg/d.

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